

WHAT IS CLAIMED IS:

1. A molecule comprising the antigen-binding portion of an isolated antibody which has an increased affinity for a receptor protein tyrosine kinase and which blocks constitutive activation of said receptor protein tyrosine kinase.
- 5 2. The molecule according to claim 1, wherein said molecule binds to the extracellular domain of said receptor protein tyrosine kinase.
3. The molecule according to claim 1 wherein the antibody binds the dimeric form of the receptor.
4. The molecule according to claim 1, wherein the receptor protein tyrosine kinase is  
10 selected from the group consisting of EGFR/ErbB1, ErbB2/HER2/Neu, ErbB/HER3, ErbB4/HER4, IGF-1R, PDGFR- $\alpha$ , PDGFR- $\beta$ , CSF-1R, kit/SCFR, Flk2/FH3, Flk1/VEGFR1, Flk1/VEGFR2, Flt4/VEGFR3, FGFR1, FGFR2/K-SAM, FGFR3, FGFR4, TrkA, TrkC, HGFR, RON, EphA2, EphB2, EphB4, Axl, TIE/TIE1, Tek/TIE2, Ret, ROS, and Alk, and heterodimeric combinations thereof.
- 15 5. The molecule according to claim 4, wherein said receptor protein tyrosine kinase is a fibroblast growth factor receptor (FGFR).
6. The molecule according to claim 5, wherein said FGFR is FGFR3.
7. The molecule according to claim 1, comprising a V<sub>H</sub> region and a V<sub>L</sub> region, respectively,  
20 selected from SEQ ID NO:103 and SEQ ID NO:92; SEQ ID NO:105 and SEQ ID NO:94; and SEQ ID NO:113 and SEQ ID NO:102.
8. The molecule according to claim 1, comprising a V<sub>H</sub>-CDR3 region and a V<sub>L</sub>-CDR3 region, respectively, selected from SEQ ID NO: 8 and SEQ ID NO: 9; SEQ ID NO: 12 and SEQ ID NO:13; and SEQ ID NO: 24 and SEQ ID NO:25.
9. The molecule according to claim 8, comprising a V<sub>H</sub>-CDR3 region and a V<sub>L</sub>-CDR3  
25 region having SEQ ID NO:24 and SEQ ID NO:25, respectively.
10. A pharmaceutical composition, comprising as an active ingredient at least one molecule according to claim 1 and a pharmaceutically acceptable carrier, excipient, or auxiliary agent.
11. An isolated nucleic acid molecule, comprising a polynucleotide sequence selected from  
30 SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:84, SEQ ID NO:89 and

SEQ ID NO:91 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

12. An isolated nucleic acid molecule, comprising polynucleotide sequences encoding a V<sub>H</sub> region and a V<sub>L</sub> region, respectively, selected from SEQ ID NO: 84 and SEQ ID NO:74; SEQ ID NO: 89 and SEQ ID NO:75; and SEQ ID NO: 91 and SEQ ID NO:76 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

13. An isolated nucleic acid molecule, comprising a polynucleotide sequence selected from SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:50 and SEQ ID NO:51 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

14. An isolated nucleic acid molecule, comprising polynucleotide sequences encoding a V<sub>H</sub>-CDR3 region and a V<sub>L</sub>-CDR3 region, respectively, selected from SEQ ID NO:30 and SEQ ID NO:31; SEQ ID NO: 34 and SEQ ID NO:35 and SEQ ID NO:50 and SEQ ID NO:51 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

15. A molecule comprising the antigen-binding portion of an antibody which binds to a fibroblast growth factor receptor (FGFR) and which blocks ligand-dependent activation of the FGFR.

16. The molecule according to claim 15, wherein said molecule binds to the extracellular domain of said FGFR.

17. The molecule according to claim 16, wherein said FGFR is FGFR3.

18. The molecule according to claim 15, comprising a V<sub>H</sub> region and a V<sub>L</sub> region, respectively, selected from SEQ ID NO:104 and SEQ ID NO:93; SEQ ID NO:106 and SEQ ID NO:95; SEQ ID NO:107 and SEQ ID NO:96; SEQ ID NO:108 and SEQ ID NO:97; SEQ ID NO:109 and SEQ ID NO:98; SEQ ID NO:110 and SEQ ID NO:99; SEQ ID NO:111 and SEQ ID NO:100 and SEQ ID NO:112 and SEQ ID NO:101.

19. A nucleic acid molecule according to claim 18, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.

20. The molecule according to claim 15, comprising a V<sub>H</sub>-CDR3 region and a V<sub>L</sub>-CDR3 region selected from SEQ ID NO:10 and SEQ ID NO:11; SEQ ID NO:14 and SEQ ID NO:15; SEQ ID NO:16 and SEQ ID NO:17; SEQ ID NO:18 and SEQ ID NO:19; SEQ ID

NO:20 and SEQ ID NO:21; SEQ ID NO:22 and SEQ ID NO:23; SEQ ID NO:26 and SEQ ID NO:27 and SEQ ID NO:28 and SEQ ID NO:29.

21. A nucleic acid molecule according to claim 20, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.

22. A pharmaceutical composition, comprising as an active ingredient at least one molecule according to claim 15 and a pharmaceutically acceptable carrier, excipient, or auxiliary agent.

23. An isolated nucleic acid molecule, comprising a polynucleotide sequence selected from SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:86 and SEQ ID NO:87 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

24. A nucleic acid molecule according to claim 23, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.

25. An isolated nucleic acid molecule, comprising polynucleotide sequences encoding a  $V_H$  region and a  $V_L$  region, respectively, selected from SEQ ID NO:85 and SEQ ID NO:70; SEQ ID NO:78 and SEQ ID NO:67; SEQ ID NO:79 and SEQ ID NO:64; SEQ ID NO:86 and SEQ ID NO:71; SEQ ID NO:80 and SEQ ID NO:62; SEQ ID NO:87 and SEQ ID NO:65; SEQ ID NO:82 and SEQ ID NO:73 and SEQ ID NO:83 and SEQ ID NO:69 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

26. A nucleic acid molecule according to claim 25, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.

27. An isolated nucleic acid molecule, comprising a polynucleotide sequence selected from SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48 and SEQ ID NO:49 or a polynucleotide sequence hybridizing under high stringency conditions thereto.

28. A nucleic acid molecule according to claim 27, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.

29. An isolated nucleic acid molecule, comprising polynucleotide sequences encoding a V<sub>H</sub>-CDR3 DNA region and a V<sub>L</sub>-CDR3 DNA region, respectively, selected from SEQ ID NO:32 and SEQ ID NO:33; SEQ ID NO:36 and SEQ ID NO:37 and SEQ ID NO:38 and SEQ ID NO:39; SEQ ID NO:40 and SEQ ID NO:41; SEQ ID NO:42 and SEQ ID NO:43; SEQ ID NO: 44 and SEQ ID NO:45; SEQ ID NO:46 and SEQ ID NO:47 and SEQ ID NO:48 and SEQ ID NO:49 or a polynucleotide sequence hybridizing under high stringency conditions thereto.
30. A nucleic acid molecule according to claim 29, wherein the nucleic acid molecule is in a vector or a host cell comprising a vector.
31. A kit comprising the molecule of claim 1 or a molecule comprising the antigen-binding portion of an antibody which binds to a fibroblast growth factor receptor (FGFR) and which blocks ligand-dependent activation of the FGFR, the kit further comprising at least one reagent suitable for detecting the presence of said molecule when bound to said receptor protein tyrosine kinase and instructions for use.
32. A method for treating or inhibiting a skeletal dysplasia or a craniosynostosis disorder, comprising administering a therapeutically effective amount of the pharmaceutical composition to a subject in need thereof, wherein the pharmaceutical composition is according to claim 10 or is a pharmaceutical composition comprising as an active ingredient at least one molecule that is an antigen-binding portion of an antibody which binds to a fibroblast growth factor receptor (FGFR) and which blocks ligand-dependent activation of the FGFR.
33. The method according to claim 32, wherein the skeletal dysplasia is selected from achondroplasia, thanatophoric dysplasia (TD), hypochondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) dysplasia.
34. The method according to claim 33, wherein said skeletal dysplasia is achondroplasia.
35. The method according to claim 32, wherein the craniosynostosis disorder is Muenke coronal craniosynostosis or Crouzon syndrome with acanthosis nigricans.
36. The method according to claim 32, wherein the disorder is associated with constitutive activation of a receptor protein tyrosine kinase or with ligand-dependent activation of a receptor protein tyrosine kinase.
37. The method according to claim 36, wherein the receptor protein tyrosine kinase is FGFR3.

38. A method for treating or inhibiting a cell proliferative disease or disorder associated with abnormal RPTK activity, comprising administering a therapeutically effective amount of the pharmaceutical composition to a subject in need thereof, wherein the pharmaceutical composition is according to claim 10 or is a pharmaceutical composition comprising as an active ingredient at least one molecule that is an antigen-binding portion of an antibody which binds to a fibroblast growth factor receptor (FGFR) and which blocks ligand-dependent activation of the FGFR.
39. The method according to claim 38, wherein the cell proliferative disease or disorder is selected from solid tumors, non-solid cancer or tumor progression,
40. The method according to claim 39, wherein the tumor progression is the progression of transitional cell carcinoma, mammary carcinoma, osteosarcoma or chondrosarcoma.
41. The method according to claim 39, wherein the non-solid cancer is a hematopoietic malignancy.
42. The method according to claim 41, wherein the hematopoietic malignancy is multiple myeloma.
43. The method according to claim 38, wherein the disorder is associated with the action of a constitutively activated receptor protein tyrosine kinase or with ligand-dependent activation of a receptor protein tyrosine kinase.
44. A method for screening a molecule comprising the antigen-binding portion of an antibody which blocks ligand-independent or ligand-dependent activation of a receptor protein tyrosine kinase, comprising:
- providing a library of antigen binding fragments;
  - screening a library of antigen binding fragments for binding to a dimeric form of a receptor protein tyrosine kinase;
  - identifying an antigen binding fragment which binds to the dimeric form of the receptor protein tyrosine kinase as a candidate molecule for blocking constitutive activation of the receptor protein tyrosine kinase; and
  - determining whether the candidate molecule blocks constitutive and or ligand-dependent activation of the receptor protein tyrosine kinase in a cell.
45. The method according to claim 44, wherein said receptor protein tyrosine kinase is selected from the group consisting of EGFR/ErbB1, ErbB2/HER2/Neu, ErbB/HER3,

ErbB4/HER4, IGF-1R, PDGFR- $\alpha$ , PDGFR- $\beta$ , CSF-1R, kit/SCFR, Flk2/FH3, Flk1/VEGFR1, Flk1/VEGFR2, Flt4/VEGFR3, FGFR1, FGFR2/K-SAM, FGFR3, FGFR4, TrkA, TrkC, HGFR, RON, EphA2, EphB2, EphB4, Axl, TIE/TIE1, Tek/TIE2, Ret, ROS, and Alk, and heterodimeric combinations thereof.

- 5      46. The method according to claim 45, wherein said receptor protein tyrosine kinase a fibroblast growth factor receptor.
47. The method according to claim 46, wherein said fibroblast growth factor receptor is FGFR3.

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